Nonsteroidal Anti-inflammatory Drugs
Proposed Guidelines for Monitoring Toxicity

THOMAS M. BUSH, MD; TAMMI L. SHLOTZHAUER, MD; *and* KENT IMAI, MD, *San Jose, California*

The most common toxicities of nonsteroidal anti-inflammatory drugs (NSAIDs) are gastropathy, renal dysfunction, and liver function abnormalities. We outline an approach to monitoring patients on long-term NSAID therapy, focusing on the early detection of complications.

Gastropathy caused by NSAID use is more common in elderly patients or those with a history of dyspepsia, peptic ulcer disease, or alcohol abuse. Fecal occult blood testing and hemograms are less accurate in detecting gastropathy than direct visualization but are convenient and relatively inexpensive. We recommend the periodic use of these tests to detect NSAID-induced acute or chronic blood loss. Renal toxicity is seen in patients with preexisting renal disease or functional volume depletion and in the elderly. Complications include renal insufficiency, hyponatremia, hyperkalemia, and proteinuria. Renal function should be monitored during the first few weeks of NSAID therapy, especially in high-risk patients, with periodic testing thereafter. Hepatic toxicity is less common but warrants occasional determinations of alanine aminotransferase levels. Elderly patients and those with renal insufficiency or alcohol abuse have a higher risk of complications.

Nonsteroidal anti-inflammatory drugs should be used cautiously in those patients at high risk for complications. Strategies can be used to limit toxicity. Patients taking these drugs long term should be monitored periodically for signs of blood loss, renal dysfunction, and hepatic dysfunction.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are taken by approximately 10% of patients.[1] Though generally well tolerated, various toxic effects can occur. Rashes and central nervous system toxicity are generally mild reactions detected easily by history and physical examination.[2,3] Pulmonary and idiosyncratic hematologic toxicities are largely unpredictable but fortunately rare.[3] Gastropathy, renal dysfunction, and liver function abnormalities are relatively common and often symptomatic only after serious toxic reactions have occurred.[4-6] We will review the incidence of these three common NSAID toxicities and propose an approach to appropriate monitoring.

Gastropathy

Incidence

Upper gastrointestinal (GI) tract bleeding is the most common serious complication of NSAID use. Barrier and Hirschowitz have reviewed endoscopic studies that uniformly show a high rate of gastric erosions and ulcers in patients taking NSAIDs.[4] Nearly a third (30%) of patients have dyspepsia. Endoscopy of these patients shows 20% with normal mucosa, 50% with erosions and petechiae, and 30% with gastric ulcers. In 70% of patients, dyspepsia does not develop. In these patients, the findings on endoscopy are a normal mucosa in 50%, erosions and petechiae in 45%, and gastric ulcers in 5%. Therefore, gastric ulcers will develop in about 12.5% of patients on NSAID therapy, a third of whom are asymptomatic.

Despite the high rate of gastric lesions seen on endoscopy, the rate of clinical bleeding in patients taking NSAIDs in a large retrospective study by Carson and co-workers was relatively low: 1.5 substantial upper GI bleeding episodes per 1,000 patient-years on NSAID therapy versus 1 per 1,000 patient-years without NSAID use.[1] This reflects a low risk for the average patient using NSAIDs. The rate of upper GI tract bleeding in patients with multiple risk factors is probably considerably higher.

Risk Factors

Well-established risk factors for serious upper GI bleeding on NSAID therapy include being older than 60 years,[1] a history of peptic ulcer disease, dyspepsia with NSAID use,[4] cigarette[7] and alcohol use, high-dose and prolonged NSAID use,[1] and serious concomitant disease. Graham and Smith did not find low-dose aspirin prophylaxis to be associated with a higher risk of upper GI bleeding.[8]

Monitoring

The diagnostic tests that could detect clinically significant NSAID-induced gastropathy include fecal occult blood testing, hemograms, upper GI tract roentgenograms, and upper GI endoscopy.

Fecal occult blood testing is less sensitive for upper GI tract blood loss than for lower GI tract blood loss. Ostrow and colleagues have shown that 25 ml of gastric blood loss is required for Hemoccult detection, whereas Hemoccult screening detects 5 ml per day of colonic blood loss.[9] Patients using NSAIDs who have a positive Hemoccult test were found by Bahrt and associates to have more colonic neoplasms than upper GI ulcers.[10]

From the Department of Medicine, Divisions of Rheumatology (Drs Bush and Shlotzhauer) and Primary Care (Drs Bush and Imai), Santa Clara Valley Medical Center, San Jose, California.

Reprint requests to Thomas M. Bush, MD, Santa Clara Valley Medical Center, 750 S Bascom Ave, San Jose, CA 95128.

ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
GI = gastrointestinal
NSAIDs = nonsteroidal anti-inflammatory drugs

Hemograms may be useful in detecting a microcytic anemia, which generally develops when blood loss exceeds 20 to 30 ml per day.[4] There has been little evidence, however, to suggest that hemograms are adequately sensitive to alert clinicians to the presence of a severe gastropathy or an impending massive upper GI hemorrhage. Doube and Collins have shown a poor correlation between hemogram results and endoscopically demonstrated gastropathy.[11]

Visualization of the upper GI tract by endoscopy is highly sensitive and specific but too expensive for routine screening. Upper GI roentgenograms are probably less useful. These studies should be reserved for patients who are still symptomatic with dyspepsia after medical therapy has been modified or for those who have evidence of blood loss.

Clinical studies have not adequately clarified the usefulness of fecal occult blood tests and hemograms in detecting early blood loss from gastropathy. Hemograms can accurately detect chronic blood loss resulting from prolonged NSAID use. Fecal occult blood tests may indicate recent heavy upper GI bleeding. Although these tests are much less accurate than direct visualization of the upper GI tract, they are noninvasive and relatively inexpensive. A positive fecal occult blood test or abnormal hemogram results should lead to a change in the patient's management (see Alternative Therapy section), even though the site of bleeding may not be immediately apparent. We recommend that patients on ongoing NSAID therapy be monitored periodically for signs of blood loss. In addition, all patients should be instructed to promptly report dyspepsia or melena.

Monitoring Guidelines for Detecting NSAID Gastropathy

- Asymptomatic or low-risk patients: An initial hemogram and fecal occult blood test should be done within the first 3 months and repeated every 6 to 12 months.
- Symptomatic or high-risk patients: An initial hemogram and fecal occult blood test should be done within the first month and repeated every 3 to 6 months; consider alternative therapies.

A notable decrease in the hemoglobin level or mean erythrocyte volume or a positive fecal occult blood test should lead to the discontinuation of NSAIDs. If a patient also complains of dyspepsia or melena, a prompt evaluation of the upper GI tract is warranted. In asymptomatic patients, the hemogram should be repeated. If there is no sign of continued blood loss, the clinician may consider the cautious use of NSAIDs that have less upper GI toxicity along with an agent to protect the gastric mucosa (see Alternative Therapy). Persistent anemia or occult bleeding may indicate an upper GI tract disorder or a malignant neoplasm of the colon in patients at risk and should be evaluated accordingly.

Renal Toxicity

Incidence

Renal toxicity due to NSAID therapy is uncommon in healthy persons, but the incidence can approach 20% in patients at high risk.[5] The most common toxic effect is hemodynamically mediated renal insufficiency due to the inhibition of renal prostaglandin synthesis.[12] A recent prospective clinical trial by Whelton and co-workers has shown that in patients with renal insufficiency, an abrupt increase in creatinine levels can occur within seven to ten days of the initiation of a regimen of a short-acting NSAID.[13] Gurwitz and associates found reversible azotemia in 13% of elderly patients treated with NSAIDs.[14]

TABLE 1.—*Risk Factors for Acute Renal Failure with Nonsteroidal Anti-inflammatory Drug Therapy*

Age older than 60
Atherosclerotic disease
Diabetes mellitus
Extracellular volume depletion
Hemorrhage
Diuretics
Extrarenal salt loss
Decreased effective volume
Congestive heart failure
Cirrhosis
Nephrotic syndrome
Other high renin-angiotensin states
Anesthesia
Renal artery stenosis
Sepsis
Preexisting renal parenchymal disease

The use of NSAIDs can induce hyperkalemia, which occasionally may be life threatening.[15] These drugs can also affect sodium and water balance, with sodium retention leading to edema or water retention causing hyponatremia.[12] All these effects are predictable in high-risk patients and reversible with the cessation of the drug.[14] Parenchymal diseases due to NSAID use, including the nephrotic syndrome, interstitial nephritis, and papillary necrosis, are largely unpredictable but fortunately rare. Nonsteroidal anti-inflammatory drugs can also interfere with the antihypertensive effect of diuretics and β-blockers.[12]

Risk Factors

The risk factors for acute renal insufficiency include age older than 60, vascular disease,[5] real or functional volume depletion,[14] preexisting renal insufficiency, high renin-angiotensin states, and systemic lupus erythematosus[12] (Table 1). Patients at high risk for hyperkalemia developing include elderly persons, those with preexisting renal disease, and patients taking potassium-sparing diuretics, potassium supplements, angiotensin-converting enzyme inhibitors, and β-blockers.[15] Patients at risk for hyponatremia developing are those taking thiazide diuretics.[12]

Monitoring

It has been shown that NSAIDs can interfere with renal function within the first few weeks of therapy. This effect is seen predominantly in patients with preexisting renal disease. Therefore, an initial assessment of renal function is necessary to determine a patient's risk of NSAID toxicity. Interstitial nephritis and nephrotic syndrome can occur sporadically, and a patient's hemodynamic status will vary with time. Thus, it seems appropriate to periodically monitor the renal function of patients on long-term NSAID therapy.

Monitoring Guidelines for Detecting NSAID-induced Renal Toxicity

To monitor patients for renal insufficiency, hyperkale-

mia, hyponatremia, and proteinuria due to NSAID use, we propose the following guidelines:

- Low-risk patients: Measure serum sodium, potassium, blood urea nitrogen, and creatinine levels and do a urinalysis within 3 months; repeat these studies every 6 to 12 months.
- High-risk patients: Measure serum sodium, potassium, blood urea nitrogen, and creatinine levels and do a urinalysis within 1 to 3 weeks; repeat these studies every 3 to 6 months; consider alternative therapies.

Elevated blood urea nitrogen, creatinine, or potassium levels, the appearance of proteinuria, or a decrease in the sodium concentration should lead to the discontinuation of NSAIDs. Patients should undergo a prompt clinical evaluation to screen for other causes of renal deterioration. A cautious reintroduction of NSAIDs with less renal toxicity may be attempted after a patient's renal function returns to baseline.

Hepatic Toxicity

Incidence

Paulus reported on a prospective trial of 7,000 patients taking NSAIDs.[6] Of these, 3% had persistent abnormalities (elevations) on more than one liver function test. Clinical hepatitis, cholestasis, and hepatic necrosis are rare. Abnormalities in liver function are almost always reversible with the cessation of NSAIDs.[16]

The mechanism of hepatic injury is varied. Salicylates appear to be predictable, dose-related hepatotoxins; other NSAIDs have idiosyncratic hepatic effects that may be due to hypersensitivity responses or metabolic changes. Hypersensitivity responses generally occur within the first four to six weeks. Other toxic hepatic reactions usually occur within three months.[16]

Risk Factors

Established risk factors are advanced age, renal insufficiency, multiple drug use,[6] alcohol use,[17] and higher drug doses[16] (Table 2).

Monitoring Tests

The consensus of the Food and Drug Administration's Arthritis Advisory Committee was that elevated aspartate or alanine aminotransferase (ALT) levels were an early warning of reversible liver toxicity.[6] The committee was concerned that continued NSAID use could result in more severe liver damage. Significant morbidity from NSAID-induced liver toxicity is uncommon in low-risk patients. If a prolonged course of NSAIDs is anticipated, we recommend an early evaluation of hepatic function. Periodic monitoring appears prudent in long-term NSAID users.

Monitoring Guidelines to Detect NSAID-induced Liver Toxicity

- Low risk: Initial ALT (SGPT) levels should be monitored within the first three months of therapy; repeat every 6 to 12 months.
- High risk: Initial ALT levels should be monitored within the first month of therapy; repeat every 3 to 6 months; consider alternative therapy.

A threefold elevation of the ALT level should lead to the discontinuation of NSAIDs. If the ALT level does not return to baseline, further investigation for hepatic disease is required. If the ALT level returns to normal, alternative NSAIDs could be cautiously instituted. A patient with a mild baseline ALT elevation should be monitored according to the guidelines for high-risk patients.

TABLE 2.—*Risk Factors for NSAID Hepatotoxicity*

Age older than 60
Renal insufficiency
Multiple drug use
High NSAID dosage
Prolonged NSAID therapy
Alcohol use
Systemic lupus erythematosus
Juvenile arthritis

NSAID = nonsteroidal anti-inflammatory drug

Alternative Therapy

If a patient has been determined to be at high risk for NSAID-induced gastropathy, renal toxicity, or hepatitis, various alternative therapeutic maneuvers should be considered. These include a lower dose NSAID regimen, non-NSAID analgesics, topical balms, and the use of other methods of pain relief such as physical therapy, acupuncture, and biofeedback.

For those patients who are at high risk for gastropathy, the use of NSAIDs with a lower gastrointestinal toxicity profile such as salsalate or magnesium choline trisalicylate should be considered.[18,19] Ulcers caused by NSAID use tend to be gastric and non-acid-dependent and, thus, less responsive to histamine$_2$ blockers and antacids.[20] Misoprostol, a prostaglandin analogue, has recently been shown to be effective in preventing NSAID ulcers.[21] Edelson and associates have shown that misoprostol is cost effective for prophylaxis against NSAID-induced upper gastrointestinal bleeding in high-risk patients.[22] Sucralfate has also been found in some studies to protect the gastric mucosa.[20] Omeprazole, a new proton pump inhibitor, was shown in a small clinical study by Daneshmend and colleagues to prevent aspirin-induced gastric mucosal injury.[23] Clinicians may consider the use of one of these agents in high-risk patients who require ongoing NSAID therapy.

Patients at risk for renal toxicity should also be considered for the use of salsalate or magnesium choline trisalicylate. These agents in moderate doses have less inhibition of prostaglandin synthesis and a generally safer renal profile.[19]

Summary

There are no controlled, prospective trials on the usefulness of monitoring for the early detection of NSAID-induced gastric, renal, or hepatic toxicity. We have reviewed the incidence of these complications, identified risk factors, and suggested guidelines for NSAID monitoring. All patients should be instructed in the common side effects of NSAIDs and encouraged to report any relevant symptoms. It is important to determine which patients are at high risk for NSAID toxicity. These patients should be monitored more carefully than low-risk patients, and, whenever possible, alternative therapies should be considered.

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This article is one of a series on topics in primary care in which common diagnostic or therapeutic problems encountered in primary care practice are presented. Physicians interested in contributing to the series are encouraged to contact the Special Editors.

STEPHEN M. McPHEE, MD
TERRIE MENDELSON, MD
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